Arterial thrombosis associated with heterozygous factor V Leiden disorder, hyperhomocysteinemia, and peripheral arterial disease: Importance of synergistic factors

Cameron Page, BS, Lee E. Rubin, MD, Richard J. Gusberg, MD, and **Alan Dardik, MD, PhD,**
West Haven and New Haven, Conn

A 47-year-old man with heterozygous factor V Leiden disorder and intermittent hyperhomocysteinemia developed spontaneous acute popliteal artery thrombosis. Homocysteine levels were above normal limits at presentation. Intra-arterial thrombolysis was used successfully to treat the acute thrombosis; long-term treatment included anticoagulation, folic acid, and risk factor modification. Although factor V Leiden is strongly associated with deep venous thrombosis, additional cofactors such as hyperhomocysteinemia may predispose to an increased risk of acute arterial thrombosis in areas of pre-existing peripheral arterial disease. (J Vasc Surg 2005;42:1014-8.)

Factor V Leiden (FVL) is strongly associated with deep venous thrombosis; however, additional cofactors such as hyperhomocysteinemia may predispose a patient to an increased risk of acute arterial thrombosis in areas of pre-existing peripheral arterial disease. We present the case of a patient with heterozygous factor V Leiden disorder and intermittent hyperhomocysteinemia who developed spontaneous acute popliteal artery thrombosis.

CASE REPORT

A 47-year-old man presented with a one-day history of increasing right leg supramalleolar pain; there was no history of trauma. His past medical history was significant for hypertension, hypercholesterolemia, and one-block left leg claudication, but no history of atrial fibrillation or previous myocardial infarction. He experienced a stroke 8 years before admission secondary to a spontaneous right carotid artery dissection, with residual left-sided weakness.

The patient also had a history of multiple upper- and lower-extremity venous thrombosis, with upper-extremity deep venous thrombosis (DVT) first diagnosed in his right arm 8 years before presentation and saphenous vein thrombosis 2 years before presentation. The work-up at that time determined that the patient was a heterozygous carrier of the FVL mutation. Test results for mutations of prothrombin gene G20210, protein C or S deficiency, and antithrombin III deficiency were negative. Serum homocysteine was 18.31 umol/L (normal, 5 to 15 umol/L). Antibodies for anticardiolipin and the lupus anticoagulant were not detectable.

From the Department of Surgery, VA Connecticut Healthcare System, and the Yale University School of Medicine.
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Reprint requests: Alan Dardik, MD, PhD, Yale University School of Medicine, Boyer Center for Molecular Medicine, 295 Congress Avenue, Room 436, New Haven, CT 06519 (e-mail: alan.dardik@yale.edu).
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The surgical history included an uncomplicated tonsillectomy. Medications included warfarin, 5 mg once daily, (international normalized ratio [INR] goal, 2.0 to 2.5), managed at an outpatient anticoagulation clinic; however, compliance was frequently noted to be poor. The patient continued to smoke one pack of cigarettes daily.

On physical examination, the right foot was ischemic and cool to the level of the knee. The left lower extremity was warm and well perfused. Both femoral pulses were easily palpable. The left popliteal, dorsalis pedis, and posterior tibial arteries had biphasic Doppler signals, but the right popliteal and dorsalis pedis arteries had monophasic signals, with no signal in the posterior tibial. These diminished pulses were significantly decreased from his most previously documented palpable right posterior tibial pulse. The ankle-brachial index on the right was 0.41 and 0.92 on the left. The results of a motor and sensory examination of the bilateral lower extremities were normal. Laboratory data included a prothrombin time of 14.2 seconds, corresponding to an INR of 1.4; the last INR measurement in the outpatient clinic, 3 months before this admission, was 2.2.

The patient was admitted with a diagnosis of acute arterial occlusion and treated with intravenous heparin at 1000 U/h. Ultrasound examination of his lower extremities failed to reveal any DVT. Angiography demonstrated thrombus in the distal superficial femoral and popliteal arteries (Fig 1). The thrombus was crossed with a wire, and catheter-directed thrombolysis was administered using tissue plasminogen activator (tPA) (4-mg bolus, 1.5 mg/h for 24 hours, with intra-arterial heparin, 500 U/h).

After 24 hours, the exam results improved, with a biphasic Doppler signal in both the dorsalis pedis and posterior tibial arteries. The tPA infusion was continued an additional 24 hours. Completion angiography, after 48 hours, demonstrated successful thrombolysis with underlying popliteal and tibial-peroneal trunk disease (Fig 2). The patient's hospital course was remarkable for right leg superficial cellulitis treated with a 10-day course of a cephalosporin. The patient refused prophylactic placement of an inferior vena cava filter. He was discharged home on day 8. His

Fig 1. Angiogram of right popliteal artery, initial view.

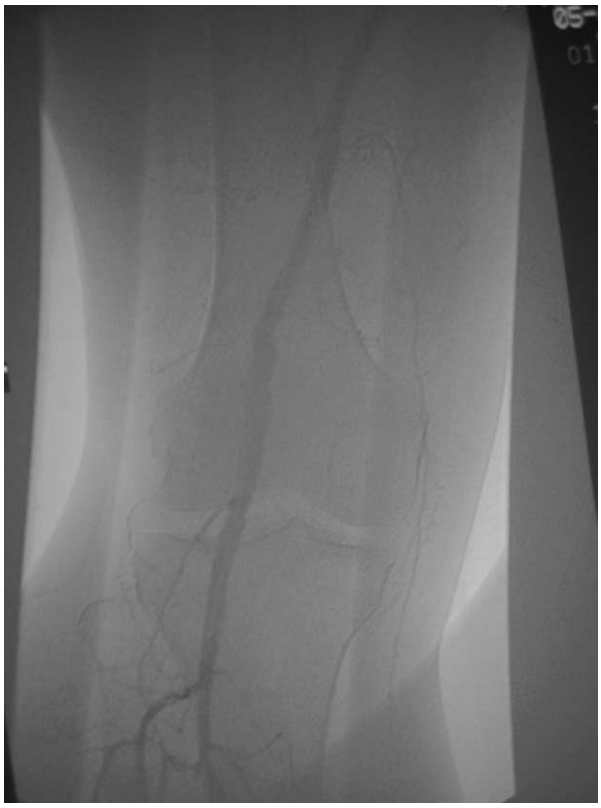

Fig 2. Angiogram of right popliteal artery after tissue plasminogen activator infusion.

discharge medications included warfarin (target INR, 2 to 3) and folic acid. The patient was counseled to quit smoking, given transdermal nicotine, and referred to our smoking cessation clinic.

DISCUSSION

FVL disorder refers to the point mutation of circulating plasma factor V, a single-chain, vitamin-K-dependent glycoprotein made in the liver. The clinical syndrome was first described in 1993 as activated protein C resistance (APC-R) syndrome, named after a group of patients with unexplained venous thromboemboli and abnormal activated partial thromboplastin time assays.[1] Since the identification of the genetic mutation responsible for APC-R syndrome occurred at the Hemostasis and Thrombosis Research Center in Leiden, Amsterdam, the condition has been referred to as factor V Leiden.

Factor V is normally prothrombotic, binding to factor X to form the prothrombin complex, which in turn activates factor II to cross-link fibrin complexes. As part of normal feedback inhibition, factor Va is deactivated by activated protein C (APC) by cleavage at amino acid 506, thus limiting the extent of clot formation.

In patients with FVL, factor Va is resistant to deactivation by APC. The isolated nature of the Leiden defect—a substitution of adenine for guanine at nucleotide 1691—is such that the abnormal factor Va is ineffective at limiting fibrin formation but is enzymatically active in its prothrombotic capacity. Thus, FVL does not predispose to clot formation in the absence of other commonly recognized risk factors such as stasis or endovascular injury.

The patient reported here had a history of smoking, which is recognized to promote thrombosis, at least in women.[2] Although this patient had a history of peripheral arterial disease, and peripheral arterial disease may promote thrombosis, the extent of coronary or peripheral arterial disease is not clearly associated with either FVL or APC activity.[3-5]

FVL typically presents with venous thrombosis, with or without pulmonary embolism. Thrombosis of deep veins (57%) is more common than in superficial vessels (43%), but the distribution is more balanced than that found in other hypercoagulable disorders.[6] In protein C deficiency, for example, 88% of venous thrombi occur in deep veins. In antithrombin deficiency, 90% of thrombi form in the deep veins; in protein C or S deficiency, 99% of thrombi occur the deep vessels. Given the much greater prevalence of FVL in relation to these other disorders, the presence of venous thrombi in superficial vessels might be a useful clinical tool as part of the hypercoagulable workup.

FVL is also associated with unexplained recurrent loss of pregnancy, as are several other hypercoagulable disorders, such as the antiphospholipid syndrome.[7] It is generally believed that this is due to thrombosis of the placental

vessels. Associations have been drawn between FVL and preeclampsia, but these data are less established.

Patients with FVL are generally not afforded special precautions when undergoing surgery. Support for this practice was established in a 1998 study of 825 subjects with and without FVL who underwent total hip or knee replacement.[8] Although the absolute incidence of venous thromboembolism, as diagnosed by venogram, was higher in FVL patients (31%) than controls (26%), the authors found no statistically significant association between FVL and venous thrombosis. More recently, however, a study of 775 patients undergoing peripheral vascular surgery found a significant difference in the rate of postoperative graft occlusion at 1 month (14% vs 7%, $P = .02$) and 1 year (22% vs 12%, $P = .02$).[9] Hypertension, smoking, and pulmonary disease were significantly more common in patients who did not possess the FVL mutation. Little research has been published on the efficacy of coagulation precautions for FVL patients, but the clear association of FVL and graft occlusion suggests that it is a worthy area of investigation.

The factor V gene is expressed codominantly. From 90% to 95% of people with the FVL mutation are heterozygotes; the remainder are homozygotes and constitute most of the recognized clinical cases. One study in Sweden of 306 people with the Leiden mutation showed that by age 33, 40% of Leiden homozygotes had a thrombotic event, whereas only 20% of heterozygotes did.[10] Data from the Leiden Thrombophilia Study demonstrated that FVL patients have an overall 6.6-fold increased risk of thrombosis compared with the general population, with homozygotes having significantly increased risk compared to heterozygotes.[11]

Numerous studies have attempted to determine the prevalence of FVL. Estimates vary between 1% and 8% of the population, with greater prevalence in Caucasians. One cross-sectional study of 4407 people reported its presence in 5.27% of Caucasians, compared with 1.27% of Hispanics, 1.23% of blacks, and 0.45% of Asians.[12] The greatest FVL prevalence appears to occur in people of Greek, Swedish, or Lebanese descent.

Despite a lack of definitive prevalence data, FVL is thought to be the most commonly inherited hypercoagulable disorder. The next most prevalent disorder, protein C deficiency, is less than half as common as FVL, occurring in an estimated one in 200 people.[13] Other thrombophilic disorders include antithrombin III deficiency, which occurs in an estimated one in 300 people,[14] and protein S deficiency, which occurs in 0.13% of the population.[15]

Despite greater prevalence, however, the risk of thrombosis as a result of FVL is much smaller than the risk associated with other inherited thrombophilias. In an Italian study, the lifetime relative risk of a venous or arterial thrombotic event, compared with the general population, was only increased 2.2-fold for FVL patients. The same risk for patients with protein C deficiency was increased 7.3-fold, for antithrombin deficiency patients 8.1-fold, and for those with protein S deficiency, the increased risk was 8.5-fold.[6]

It was previously believed that the FVL disorder, deficiencies in protein S or protein C, and antithrombin III deficiency were unique disorders with independent genetic etiologies. Recent studies have begun to demonstrate an inter-relationship among these conditions. For example, a study of families with protein S deficiency found that 39% of subjects also carried the FVL mutation.[16] In another study, 18 of 128 families (15%) with antithrombin deficiency were also FVL carriers.[17] All inherited thrombophilic disorders have not yet been linked to a single genetic locus. From a clinical standpoint, however, patients diagnosed with one thrombophilic defect clearly have greater risk for carrying a second.

It appears that for patients who carry more than one thrombophilic defect, the risk of thromboembolism is increased synergistically. In an analysis of eight case-control studies examining the effect of FVL and prothrombin 20210A defect, the odds ratio for patients heterozygous for FVL and prothrombin mutation was 4.9 and 3.8, respectively. However, the odds ratio for patients with both disorders was 20.0, far larger than even the sum of each individual risk.[18] The synergistic effect seen with multiple thrombophilic conditions is particularly germane to this case report. One factor increasing the risk of recurrent thrombotic events in this case was likely the patient's hyperhomocysteinemia.

High plasma homocysteine levels are associated with fatal and nonfatal cardiovascular events and are a modest predictor of both coronary artery disease, stroke, and symptomatic peripheral vascular disease.[19-20] In addition, hyperhomocysteinemia increases the mortality risk of patients with peripheral vascular disease: a recent large study demonstrated a 6.6-fold increase in premature mortality in patients with both peripheral vascular disease and hyperhomocysteinemia compared with the absence of these conditions.[21] Hyperhomocysteinemia and FVL disorder are also both associated with thromboembolism, with a synergistic increase in hypercoagulability when present in the same patient. A prospective study of 800 men followed for 10 years demonstrated a relative risk of venous thromboembolism (VTE) of 3.6 for FVL patients, 3.4 for patients with hyperhomocysteinemia, and 21.8 for those carrying both traits.[22]

Although the relationship between hyperhomocysteinemia and thrombosis is apparent, the mechanism is less clear. Hypotheses include smooth muscle cell proliferation, oxidative stress, nitric oxide suppression, and increased leukocyte recruitment.[23-26] Among the many pathways homocysteine appears to affect, one of the most prominent is stimulation of the prothrombotic capacity of factor V.[27] People with FVL, such as the patient reported here, have diminished ability to regulate factor Va and thus may be particularly vulnerable to high serum homocysteine levels. In addition, the role of homocysteine-induced endothelial damage in localized areas of peripheral arterial disease,

serving as the nidus for arterial thrombi, needs to be clarified.[28]

CONCLUSION

FVL is a relatively new disease. The mechanisms by which the FVL mutation disrupts coagulation and hemostasis are still being explored. No clear association has been found in the literature between FVL and arterial thrombosis, but there have been case reports of arterial thrombi in FVL patients.[29-32] Some of these cases describe association with other factors that predispose a patient to thrombosis, such as presence of lupus anticoagulant, and the postoperative period.[33-35] We report a patient with FVL and several predisposing factors for arterial thrombosis, including hyperhomocysteinemia, peripheral vascular disease, and smoking. Additional research is needed to understand the interaction of these additional factors with mutated factor V that predispose patients to arterial thrombosis.

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